General

Guideline Title

EFNS/MDS-ES recommendations for the diagnosis of Parkinson's disease.

Bibliographic Source(s)

Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, Brooks D, Burn DJ, Colosimo C, Fanciulli A, Ferreira J, Gasser T, Grandas F, Kanovsky P, Kostic V, Kulisevsky J, Oertel W, Poewe W, Reese JP, Relja M, Ruzicka E, Schrag A, Seppi K, Taba P, Vidailhet M. EFNS/MDS-ES recommendations for the diagnosis of Parkinson's disease. Eur J Neurol. 2013 Jan;20(1):16-34. [245 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The levels of evidence (Class I–IV) supporting the recommendations and ratings of recommendations (A–C) are defined at the end of the "Major Recommendations" field.

Section 1: Clinical Diagnostic Criteria for Parkinson's Disease (PD)

Only the Queen Square Brain Bank (QSBB) clinical diagnostic criteria have been validated by Hughes et al. (2002) and are therefore recommended as *probably effective* (Level B) for clinical practice.

Section 2: Genetic Testing

Available evidence provides a Level B recommendation for the use of genetic testing in the diagnosis of PD. Genetic testing for specific mutations is recommended on an individual basis, and specific features, particularly family history and age of onset, must be taken into account:

I. Testing for *alpha-synuclein (SNCA)* point mutations and gene multiplications is recommended only in families with multiple affected members in more than one generation suggestive of dominant inheritance, with early- or late-onset PD.
II. *Leucine-rich repeat kinase 2 (LRRK2)* genetic testing for counselling purposes, specifically directed at known pathogenic variants is recommended in patients with a clinical picture of typical PD and a positive family history suggestive of dominant inheritance.
III. In sporadic patients, genetic testing should be limited to the search for known *LRRK2* founder mutations in the appropriate populations (i.e., with known high mutation frequencies).
IV. Genetic testing for glucocerebrosidase (GBA) gene mutations is recommended in patients with typical PD with or without a positive family

history, limited to the known founder mutations of established pathogenic role in the appropriate populations.

V. Genetic testing of the *parkin, PINK1* and *DJ-1* genes for counselling purposes is recommended in patients with typical PD and positive family history compatible with recessive inheritance, particularly when the disease onset is before the age of 50 years. For sporadic cases, *parkin, PINK1* and *DJ-1* genetic testing is recommended when onset is very early, particularly before the age of 40.
VI. Testing of the *ATP13A2, PLA2G6* and *FBXO7* genes might be considered in cases with very-early-onset PD, if no mutation in *parkin, PINK1* and *DJ-1* gene has been found.

Section 3: Autonomic Function Tests

Neurophysiological Assessment of Autonomic Function

Autonomic function tests (AFTs) are principally helpful to detect autonomic impairments in patients with PD. Some dysautonomic features, like orthostatic hypotension (OH) or post-void residual volume, have important therapeutic implications. However, at the moment, there is insufficient evidence to provide a level of recommendation for AFTs in PD.

Section 4: Olfactory Tests

Olfactory testing differentiates PD from:

I. Atypical and secondary parkinsonian disorders (Level A)
II. Recessive forms of PD (Level A)

Current evidence suggests that olfactory testing may be considered as a diagnostic screening procedure (Level A), but not as an indicator of disease progression (Level B) in PD. Olfactory testing is a sensitive screening test for pre-motor PD (Level A), but not specific. Thus, olfactory testing can be envisioned in a screening battery for PD. If hyposmia is detected, then other specific tests for PD should follow.

Section 5: Drug Challenge Tests

Drug challenge tests are not recommended for the diagnosis of de novo parkinsonian patients. There is insufficient evidence to support their role in the differential diagnosis between PD and other parkinsonian syndromes.

Section 6: Neurophysiological Tests

No recommendation can be given on neurophysiological tests because of the low evidence level of the available studies.

Section 7: Neuropsychological Tests

An assessment of neuropsychological functioning in a person presenting with parkinsonism suspected of being PD is recommended (Level A) and should include:

I. A collateral history from a reliable carer
II. A brief assessment of cognition
III. Screening for rapid eye movement (REM) sleep behaviour disorder (RBD), psychotic manifestations and severe depression

Section 8: Neuroimaging

Transcranial Sonography (TCS)

TCS is recommended (Level A) for:

I. Differential diagnosis of PD from atypical parkinsonian syndromes (APS) and secondary parkinsonian syndromes
II. Early diagnosis of PD
III. Detection of subjects at risk for PD

The technique is so far not universally used and requires some expertise. Because specificity of TCS for the development of PD is limited, TCS should be used in conjunction with other screening tests.

Magnetic Resonance Imaging

The Task Force concludes that conventional magnetic resonance imaging (cMRI) at 1.5 T is principally helpful to exclude symptomatic parkinsonism due to other pathologies (Level B).

1.5-T cMRI is also useful in the differentiation of PD from APS as follows:

I. Multiple system atrophy (MSA) signs – putaminal atrophy and rim sign, pontocerebellar atrophy, middle cerebellar peduncle (MCP) hyperintensity and hot cross bun sign (all Level A)
II. Progressive supranuclear palsy (PSP) signs – midbrain atrophy and hummingbird sign (both Level B), superior cerebellar peduncle (SCP) atrophy (Level C)

Specificity of these abnormalities to differentiate APS from PD is considered quite high, whereas sensitivity, particularly in early disease stages, seems to be insufficient. A normal routine 1.5-T cMRI does not exclude MSA or PSP, if the clinical presentation is suggestive and supported by the current diagnostic criteria.

Abnormalities on diffusion-weighted imaging (DWI) at 1.5 T including diffusivity changes in:

I. Putamen in patients with APS versus PD in early disease stages (especially MSA-parkinsonian subtype [MSA-P], Level A)
II. SCP in patients with PSP (Level B) have been described as markers, which can point the diagnosis towards MSA or PSP instead of PD

Newer quantitative imaging techniques implemented on 3-T systems have shown promising results. However, they require further confirmatory studies.

Single Photon Emission Tomography

Dopamine transporter-single photon emission tomography (DaTscan-SPECT) is registered in Europe and the United States for the differential diagnosis between degenerative parkinsonism and essential tremor (Level A). More specifically, DaTscan-SPECT is indicated in the presence of significant diagnostic uncertainty and particularly in patients presenting atypical tremor manifestations. Cardiac [^{123}I] meta-iodobenzylguanidine (MIBG)/SPECT imaging may assist in the differential diagnosis of PD versus APS (Level A).

All other SPECT imaging studies do not fulfill registration standards and cannot be recommended for routine clinical use.

Positron Emission Tomography (PET)

None of the reviewed PET studies has been performed according to regulatory standards with the exception of the study by Whone et al. (2003). Therefore, the Task Force cannot make any formal recommendation for the routine use of PET studies in the diagnostic work-up of PD.

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation.

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls).

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Parkinson's disease

Guideline Category

Diagnosis

Screening

Clinical Specialty

Family Practice

Medical Genetics

Neurology

Radiology

Intended Users

Advanced Practice Nurses

Nurses

Physicians

Guideline Objective(s)

To develop guidelines for the diagnosis of Parkinson's disease to be applied across Europe

Target Population

Individuals at risk for Parkinson's disease

Interventions and Practices Considered

1. Clinical diagnostic criteria (Queen Square Brain Bank [QSBB])
2. Genetic testing for the following mutations:
    - *Alpha-synuclein (SNCA)*
    - *Leucine-rich repeat kinase 2 (LRRK2)*
    - *Glucocerebrosidase (GBA)*
    - *parkin*, *PINK1*, and *DJ-1*
    - *ATP13A2*, *PLA2G6*, and *FBXO7*

3. Olfactory tests
4. Neuropsychological tests
    - Collateral history
    - Brief assessment of cognition
    - Screening for rapid eye movement (REM) sleep behavior disorder (RBD), psychotic manifestations, and severe depression
5. Neuroimaging
    - Transcranial sonography (TCS)
    - Conventional magnetic resonance imaging (cMRI)
    - Dopamine transporter-single photon emission tomography (DaTscan-SPECT)
    - Cardiac [^{123}I] meta-iodobenzylguanidine (MIBG)/SPECT imaging

Note: The following interventions were considered but not recommended: autonomic function tests, drug challenge tests, neurophysiological tests, SPECT imaging other than DaTscan-SPECT or cardiac [^{123}I] meta-iodobenzylguanidine (MIBG)/SPECT, positron emission tomography (PET).

Major Outcomes Considered

Sensitivity and specificity of diagnostic tests

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

This European Federation of Neurological Societies/Movement Disorder Society–European Section (EFNS/MDS–ES) Task Force report is divided into nine sections addressing key aspects of the diagnostic work-up of patients presenting with parkinsonism.

Groups of experts were allocated to each section and asked to provide an evidence-based recommendation level for the assigned diagnostic tool. To this end, MEDLINE, EMBASE and Cochrane libraries were searched for relevant citations up to June 2011.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation.

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls).

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This European Federation of Neurological Societies/Movement Disorder Society–European Section (EFNS/MDS–ES) Task Force report is divided into nine sections addressing key aspects of the diagnostic work-up of patients presenting with parkinsonism.

Groups of experts were allocated to each section and asked to provide an evidence-based recommendation level for the assigned diagnostic tool. Consensus on the guidelines was finally reached within the Task Force.

Rating Scheme for the Strength of the Recommendations

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Cost Analysis

Economic Issues

Cost-effectiveness data are scarce in Parkinson's disease (PD). Only ^{123}I-2beta-carbometoxy-3beta-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (^{123}I-FP-CIT) single photon emission tomography (SPECT) was assessed in three jurisdictions (Italy, Belgium and Germany). In all three publications, the authors came to the conclusion that ^{123}I-FP-CIT SPECT has to be regarded as cost-effective investigation for the differential diagnosis of essential tremor from parkinsonian disorders, if used as a confirmatory test in drug-naive patients with a positive clinical examination. There are insufficient cost-effectiveness data for all the other diagnostic modalities reviewed in this statement. This is an area of unmet need deserving future investigations.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

References Supporting the Recommendations

Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain. 2002 Apr;125(Pt 4):861-70. PubMed

Whone AL, Watts RL, Stoessl AJ, Davis M, Reske S, Nahmias C, Lang AE, Rascol O, Ribeiro MJ, Remy P, Poewe WH, Hauser RA, Brooks DJ, REAL-PET Study Group. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. Ann Neurol. 2003 Jul;54(1):93-101. PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis of Parkinson's disease

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

This guideline provides the view of an expert Task Force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

Implementation of the Guideline

Description of Implementation Strategy

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints

of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

Implementation Tools

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Jan

Guideline Developer(s)

European Academy of Neurology - Medical Specialty Society

Movement Disorders Society--European Section - Professional Association

Source(s) of Funding

European Federation of Neurological Societies

Guideline Committee

European Federation of Neurological Societies/Movement Disorder Society–European Section Task Force on Diagnosis of Parkinson's Disease

Composition of Group That Authored the Guideline

Task Force Members: A. Berardelli, Dipartimento di Neurologia e Psichiatria and IRCCS NEUROMED Institute, Sapienza, Università di Roma, Rome, Italy; G.K. Wenning, Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; A. Antonini, Parkinson's disease and Movement Disorders Unit IRCCS, San Camillo, Venice, Milan, Italy; D. Berg, Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research, German Center for Neurodegenerative Diseases, University of Tübingen and DZNE, Tübingen, Germany; B.R. Bloem, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Radboud University Nijmegen Medical Center, Nijmegen; V. Bonifati, Department of Clinical Genetics, Erasmus MC, Rotterdam, The Netherlands; D. Brooks, Department of Clinical Neuroscience, Imperial College London, Hammersmith Hospital, London, UK; D.J. Burn, Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK; C. Colosimo, Dipartimento di Neurologia e Psichiatria, Sapienza, Università di Roma, Rome, Italy; A. Fanciulli, Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; J. Ferreira, Centro De Estudos Egas Moniz, Faculdade De Medicina De Lisboa, Lisbon, Portugal; T. Gasser, Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research, German Center for Neurodegenerative Diseases, University of Tübingen and DZNE, Tübingen, Germany; F. Grandas, Movement Disorders Research Unit, Hospital Universitario Gregorio Marañón, Madrid, Spain; P. Kanovsky, Department of Neurology, Palacky University, Olomouc, Czech Republic; V. Kostic, Institute of Neurology CCS, School of Medicine, University of Belgrade, Belgrade, Serbia; J. Kulisevsky, Movement Disorders Unit, Department of Neurology, Sant Pau Hospital, Universitat Autonoma de Barcelona and Ciberned, Barcelona, Spain; W. Oertel, Department of Neurology, Centre of Nervous Diseases, Philipps-University of Marburg, Marburg, Germany; W. Poewe, Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; J.-P. Reese, Institut für Medizinische Soziologie, Deutschland, Germany; M. Relja, Department of Neurology, Movement Disorders Centre, School of Medicine and University Hospital Centre, University of Zagreb, Zagreb, Croatia; E. Ruzicka, 1st Faculty of Medicine and General University Hospital in Prague, Charles University in Prague, Praha, Czech Republic; A. Schrag, Institute of Neurology, University College London, London, UK; K. Seppi, Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; P. Taba, Department of Neurology and Neurosurgery, University of Tartu, Tartu, Estonia; M. Vidailhet, Pôle des Maladies du Système Nerveux et CRICM UPMC/INSERM UMR_S975 CNRS UMR7225, Fédération de Neurologie, Hôpital de la Salpêtrière, Paris, France

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site .

Availability of Companion Documents

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site .
- Continuing Medical Education questions are available to registered users from the European Journal of Neurology Web site .

Patient Resources

None available

NGC Status

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